Prevention of cardiac hypertrophy in mice by calcineurin inhibition.

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Hypertrophic **cardiomyopathy** (HCM) is an inherited form of heart disease that affects 1 in 500 individuals. Here it is shown that calcineurin, a calcium-regulated phosphatase, plays a critical role in the pathogenesis of HCM. **Administration** of the calcineurin inhibitors **cyclosporin** and FK506 prevented disease in mice that were genetically predisposed to develop HCM as a result of aberrant expression of tropomodulin, myosin light chain-2, or fetal beta-tropomyosin in the heart. **Cyclosporin** had a similar effect in a rat model of pressure-overload hypertrophy. These results suggest that calcineurin inhibitors merit investigation as potential therapeutics for certain forms of human heart disease.

Long-term follow-up and complications after cardiac transplantation.

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Cardiac transplantation has become an established therapy for **cardiomyopathy** and other irreversible cardiac diseases. Improvements in immunosuppression and management of infections has improved long-term survival following transplantation. The role of the primary care physician in the care of recipients will be expanding. Transplant recipients receive close outpatient follow-up after discharge, primarily to monitor immunosuppression through laboratory evaluation and drug levels, monitor for rejection through endomyocardial biopsy, and to assess for any signs of opportunistic infection. The foundation for long-term immunosuppression is **administration** of **cyclosporin** , azathioprine and corticosteroids. Antibiotic prophylaxis is used to decrease the chance of infection with cytomegalovirus, Pneumocystis, Candida, Toxoplasma, and other opportunistic organisms. The major long-term complications include rejection, infection, hypertension, renal dysfunction, lipid abnormalities, and accelerated coronary atherosclerosis. This review provides an overview of the short- and long-term follow-up of the cardiac transplant recipient, including routine care as well as detection and management of the common complications.

May **1993** ,

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Mitochondrial permeability transition in CNS trauma: Cause or effect of neuronal cell death?
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ABSTRACT: Experimental traumatic brain injury (TBI) and spinal cord injury (SCI) result in a rapid and significant necrosis of neuronal tissue at the site of injury. In the ensuing hours and days, secondary injury exacerbates the primary damage, resulting in significant neurologic dysfunction. It is believed that alterations in excitatory amino acids (EAA), increased reactive oxygen species (ROS), and the disruption of Ca2+ homeostasis are major factors contributing to the ensuing neuropathology. Mitochondria serve as the powerhouse of the cell by maintaining ratios of ATP:ADP that thermodynamically favor the hydrolysis of ATP to ADP + Pi, yet a byproduct of this process is the generation of ROS. Proton-pumping by components of the electron transport system (ETS) generates a membrane potential (DELTAPSI) that can then be used to phosphorylate ADP or sequester Ca2+ out of the cytosol into the mitochondrial matrix. This allows mitochondria to act as cellular Ca2+ sinks and to be in phase with changes in cytosolic Ca2+ levels. Under extreme loads of Ca2+, however, opening of the mitochondrial permeability transition pore (mPTP) results in the extrusion of mitochondrial Ca2+ and other high- and low-molecular weight components. This catastrophic event discharges DELTAPSI and uncouples the ETS from ATP production. Cyclosporin A (CsA), a potent immunosuppressive drug, inhibits mitochondrial permeability transition (mPT) by binding to matrix **cyclophilin D** and blocking its binding to the adenine nucleotide translocator. Peripherally **administered** CsA attenuates mitochondrial dysfunction and neuronal damage in an experimental rodent model of TBI, in a dose-dependent manner. The underlying mechanism of neuroprotection afforded by CsA is most likely via interaction with the mPTP because the immunosuppressant FK506, which has no effect on the mPT, was not neuroprotective. When CsA was **administrated** after experimental SCI at the same dosage and regimen used TBI paradigms, however, it had no beneficial neuroprotective effects. This review takes a comprehensive and critical look at the evidence supporting the role for mPT in central nervous system (CNS) trauma and highlights the differential responses of CNS mitochondria to mPT induction and the implications this has for therapeutically targeting the mPT in TBI and SCI. Copyright 2004 Wiley-Liss. Inc.

...ABSTRACT: A (CsA), a potent immunosuppressive drug, inhibits mitochondrial permeability transition (mPT) by binding to matrix **cyclophilin D** and blocking its binding to the adenine nucleotide translocator. Peripherally **administered** CsA attenuates mitochondrial dysfunction and neuronal damage in an experimental rodent model of TBI,

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